DOCKET NO.: 133584.00901 (IBIS-0007) **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of: **Ecker, Griffey, Crooke, Sampath, Swayze, Hofstadler, and McNeil**

Title: **Modulation Of Molecular Interaction Sites On RNA And Other Biomolecules**

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Examiner: **John S. Brusca**

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APPELLANT'S APPEAL BRIEF PURSUANT TO 37 CFR §41.37

Appellant hereby submits one copy of the present Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Notice dated June 30, 2009, the Final Rejection dated November 17, 2008, and the Advisory Action dated February 4, 2009 in regard to the above-identified application. A Notice of Appeal was timely filed February 18, 2009. The period for filing the Appeal Brief has been extended, by enclosure of a petition and appropriate fee, to and through May 18, 2009.

I. Real Party In Interest

The real party in interest in the above-identified patent application is Isis Pharmaceuticals, Inc. of Carlsbad, California. An Assignment to Isis Pharmaceuticals, Inc. was recorded at Reel 009631, Frame 0445 on December 10, 1998. The real party in interest is referred to herein as "Appellant."

II. Related Appeals And Interferences

Appellant's undersigned attorney is unaware of any related appeal or interference that will affect or be affected by or have any bearing on the decision rendered in this appeal.

III. Status Of Claims

Claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 remain pending and rejected, and are now on appeal -- the appealed claims appear in the Claims Appendix. All other claims have been canceled.

IV. Status Of Amendments

In response to the Final Rejection dated November 17, 2008, no amendments were made to the claims. All amendments during prosecution have been entered.

V. Summary Of Claimed Subject Matter

Referring to Claim 19, Appellant's claimed subject matter relates to a method of identifying a compound that binds to a human target RNA comprising (page 18, lines 29-30; page 26, line 29 to page 27, line 3): generating *in silico* a virtual library of compounds (page 18, line 32 to page 19, line 1; page 19, lines 11-13; page 61, lines 28-32; page 64, lines 5-12) and an *in silico* three dimensional representation of a molecular interaction site within the target RNA (page 18, lines 31-32; page 19, lines 10-11; page 61, lines 28-32; page 64, lines 5-12), wherein the molecular interaction site is less than 30 nucleotides (page 16, lines 1-2); comparing *in silico* the three dimensional representations of the molecular interaction site with members of the virtual library to generate a hierarchy of compounds ranked in accordance with their ability to form physical interactions with the molecular interaction site (page 19, lines 13-16; page 97, lines 12-21; page 99, line 27 to page 100, line 8); synthesizing the highly ranked members of the hierarchy (page 100, lines 22-31); and testing the highly ranked members to determine their ability to interact with the molecular interaction site by (page 100, line 30 to page 101, line 9): contacting the target RNA with at least one of the highly ranked members to provide a complex between the target RNA and the member(s), ionizing the complex, fragmenting the ionized complex, and determining whether highly ranked members bind to the molecular interaction site of the target RNA (page 20, line 28 to page 21, line 5; page 118, line 17 to page 120, line 10; page 126, lines 8-16); and thereby identifying a compound that binds to a RNA target.

Referring to Claim 26, Appellant's claimed subject matter also relates to a method of identifying a compound that binds to a human target RNA comprising (page 18, lines 29-30; page 26, line 29 to page 27, line 3): identifying *in silico* at least one molecular interaction site less than 30 nucleotides in length on the target RNA by comparing the nucleotide sequence of the target RNA with the nucleotide sequence of a RNA from a different taxonomic species (page 16, lines 19-21; Figure 1); identifying at least one conserved region, and determining the secondary structure of the conserved region (page 16, lines 22-24; Figure 1); generating *in silico* a virtual library of compounds predicted or calculated to interact with the molecular interaction site (page 18, line 32 to page 19, line 1; page 19, lines 11-13; page 61, lines 28-32; page 64, lines 5-12); comparing *in silico* three dimensional representation of the molecular interaction site with members of the virtual library to generate a hierarchy of compounds ranked in accordance with

their ability to form physical interactions with the molecular interaction site (page 19, lines 13-16; page 97, lines 12-21; page 99, line 27 to page 100, line 8); synthesizing the highly ranked members of the hierarchy (page 100, lines 22-31); testing the highly ranked members to determine their ability to interact with the molecular interaction site (page 100, line 30 to page 101, line 9); contacting the target RNA with at least one of the highly ranked members to provide a complex between the target RNA and the member(s), ionizing the complex, fragmenting the ionized complex, and determining whether highly ranked members bind to the molecular interaction site of the target RNA (page 20, line 28 to page 21, line 5; page 118, line 17 to page 120, line 10; page 126, lines 8-16); and thereby identifying a compound that binds to a human RNA target.

Referring to Claim 32, Appellant's claimed subject matter also relates to a method of identifying a compound that binds to a human target RNA comprising (page 18, lines 29-30; page 26, line 29 to page 27, line 3): identifying at least one molecular interaction site on the target RNA, wherein the molecular interaction site is less than 30 nucleotides (page 16, lines 19-21; Figure 1); generating *in silico* a virtual library of compounds predicted or calculated to interact with the molecular interaction site (page 18, line 32 to page 19, line 1; page 19, lines 11-13; page 61, lines 28-32; page 64, lines 5-12); comparing *in silico* three dimensional representations of the molecular interaction site with members of the virtual library to generate a hierarchy of compounds ranked in accordance with their ability to form physical interactions with the molecular interaction site (page 19, lines 13-16; page 97, lines 12-21; page 99, line 27 to page 100, line 8); synthesizing the highly ranked members of the hierarchy (page 100, lines 22-31); contacting the target RNA with at least one of the highly ranked members to provide a complex between the target RNA and the member(s), ionizing the complex, fragmenting the ionized complex, and determining whether highly ranked member(s) bind to the molecular interaction site of the target RNA (page 20, line 28 to page 21, line 5; page 118, line 17 to page 120, line 10; page 126, lines 8-16); thereby identifying a compound that binds to a human RNA target.

Referring to Claim 34, Appellant's claimed subject matter also relates to a method of identifying a compound that binds to a human target RNA comprising (page 18, lines 29-30; page 26, line 29 to page 27, line 3): identifying at least one molecular interaction site of less than

30 nucleotides on the target RNA, wherein the target RNA comprises single-stranded RNA and is mRNA, premRNA, tRNA, rRNA, or snRNA (page 27, lines 1-3); generating *in silico* a virtual library of compounds predicted or calculated to interact with the molecular interaction site (page 18, line 32 to page 19, line 1; page 19, lines 11-13; page 61, lines 28-32; page 64, lines 5-12); comparing *in silico* three dimensional representation of the molecular interaction site with members of the virtual library to generate a hierarchy of compounds ranked in accordance with their ability to form physical interactions with the molecular interaction site (page 19, lines 13-16; page 97, lines 12-21; page 99, line 27 to page 100, line 8); synthesizing the highly ranked members of the hierarchy (page 100, lines 22-31); contacting the target RNA with at least one of the highly ranked members to provide a complex between the target RNA and the member(s), ionizing the complex, fragmenting the ionized complex, and determining whether highly ranked member(s) binds to the molecular interaction site of the target RNA (page 20, line 28 to page 21, line 5; page 118, line 17 to page 120, line 10; page 126, lines 8-16); thereby identifying a compound that binds to a human RNA target.

VI. Grounds of Rejection to be Reviewed on Appeal

Two grounds of rejection remain for resolution in this appeal and include:

1) whether claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 are unpatentable under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention; and

2) whether claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of the following references: 1) Murray et al., J. Computer-Aided Mol. Des., 1997, 11, 193-207 (hereinafter, the "Murray reference"), 2) U.S. Patent No. 6,337,183 (hereinafter, the "Arenas reference"), 3) Sezerman et al., Protein Sci., 1993, 2, 1827-1843 (hereinafter, the "Sezerman reference"), 4) Greig et al., J. Am. Chem. Soc., 1995, 117, 10765-10766 (hereinafter, the "Greig reference"), and 5) Hentze et al., Science, 1987, 238, 1570-1573 (hereinafter, the "Hentze reference").

VII. Argument

A. The Written Description Rejection (Grounds of Rejection 1)

The rejection of claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 (which stand or fall together for this ground of rejection) under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is improper and should be reversed because the specification provides ample written description supporting the claims.

"To satisfy the written description requirement, 'the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'" *Carnegie Mellon Univ. v. Hoffmann La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (quoting *In re Alton*, 76 F.3d 1168, 1172 (Fed. Cir. 1996)). "In other words, the applicant must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate that by disclosure in the specification of the patent." *Id.* (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991)). Such disclosure need not recite the claimed invention *in haec verba*, but it must do more than merely disclose that which would render the claimed invention obvious. *Rochester*, 358 F.3d at 923; *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67 (Fed. Cir. 1997); *see also PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-07 (Fed. Cir. 2008) (explaining that § 112, ¶1 "requires that the written description actually or inherently disclose the claim element").

The Office asserts that Appellant's specification "does not describe the structure of human target RNA sequences with an interaction site that is **less** than 30 nucleotides in length" (see, page 3 of the Final Rejection; emphasis in the Final Rejection). As a preliminary matter, Appellant is not generically claiming all RNA targets having a molecular interaction site less than 30 nucleotides. Rather, claim 19, for example, recites a method of identifying a compound that binds to a human target RNA. One step of such method recites that a three dimensional representation of a molecular interaction, less than 30 nucleotides, is generated *in silico*. The

Office mistakenly asserts that Appellant is not in possession of molecular interaction sites of less than 30 nucleotides.

First, the Office is again reminded that Appellant's specification teaches:

> Applicants' invention is directed to methods of identifying secondary structures in eukaryotic and prokaryotic RNA molecules termed "molecular interaction sites." **Molecular interaction sites are** small, usually **less than 30 nucleotides**, independently folded, functional subdomains contained within a larger RNA molecule.

(see, page 15, line 30 to page 16, line 2 of the specification). Thus, this portion of the specification alone provides ample written description showing that Appellants were in possession of the claimed invention.

Second, Appellant's specification provides ample guidance and written description for identification and/or assembly of target RNA molecules and identification of conserved regions within these molecules (see, for example, pages 26-39). These conserved regions, if possessing secondary structure, are molecular interaction sites. Appellant's specification further teaches that when generating a series of sequences, a plurality of nucleic acids having at least a portion of their nucleotide sequences which are homologous to at least an 8 to 20 nucleotide region of the target nucleic acid results (see, for example, page 34, lines 20-22). Further, Appellant teaches that the "window size" for homology can be from about 8 to about 20, or from 10-15, or about 11-12 (see, for example, page 34, lines 26-28). Appellant also teaches that a window from about 10 to about 30 nucleotides, as well as a window of 21 nucleotides can be used to identify conserved sequence regions (see, for example, page 38, lines 7-17). Again, it is these conserved regions among RNA targets that contain molecular interaction sites. Once these conserved regions are identified, Appellant's specification provides ample guidance and written description for determining whether the conserved regions have secondary structure (see, for example, pages 39-44). Thus, these portions of the specification also provide ample written description showing that Appellant was in possession of the claimed invention.

Third, Figures 40-44 of Appellant's specification relate to a 27-mer RNA target corresponding to the 16S rRNA A-site. This 27-mer is also discussed in Examples 13-16. In addition, Example 12 discusses a 5'-UTR containing a 27-mer RNA construct of the HIV TAR stem-loop bulge. These 27-mers are examples of molecular interaction sites.

Thus, Appellant's specification as a whole provides ample written description of a molecular interaction site having "less than 30 nucleotides." Indeed, Appellant's specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Appellant was in possession of the claimed invention. In view of the foregoing, Appellant respectfully requests that the rejection under 35 U.S.C. §112, first paragraph, as allegedly failing to provide sufficient written description be reversed.

A. The Obviousness Rejection (Grounds of Rejection 2)

The rejection of claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 (in which claims 26, 30, 40 and 41 are argued separately herein for this ground of rejection) under 35 U.S.C. §103(a) over the combination of the Murray, Arenas, Sezerman, Greig, and Hentze references is improper and should be reversed because combination of the cited references fails to produce the claimed invention.

The Office asserts:

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the screening method of Murray et al. by use of the RNA targets of Arenas et al. because Arenas et al. shows bioassays that screen for compounds that bind to RNA targets. It would have been further obvious to use mass spectroscopy to analyze binding strength because Sezerman shows that peptides may be analyzed in silico for binding, and Greig et al. shows that mass spectroscopy may be used to determine the binding affinity of a complex of a peptide and an oligonucleotide, and experimental determination of binding strength is an important parameter for determination of biological activity. It would have been further obvious to use the IRE target sequence of Hentze et al. because Hentze et al. shows that the human IRE RNA target sequence has a role in cell iron metabolism, and further can be used to confer regulation of translation on a mRNA of choice. Development of compounds that bind to the human IRE would allow for development of compounds that inhibit or enhance expression of wild type or recombinant genes in human cells as suggested by Arenas to allow for insights into the function of naturally occurring mRNA or to regulate gene expression of recombinant genes comprising the IRE.

(See, Final Rejection at pages 6-7).

Regarding claims 26, 30, 40 and 41, it cannot fairly be said that the combination of cited references, which does not so much as mention some features recited in the claimed methods, render the claimed methods obvious. Thus, rejection under §103 is improper because a *prima facie* case of obviousness cannot be made. *In re Payne*, 203 USPQ 245, 255 (CCPA 1979) (references relied upon to support rejection under §103 must place the claimed invention in the possession of the public). For example, claim 26 recites, in relevant part: "identifying *in silico* at least one molecular interaction site less than 30 nucleotides in length on said human target RNA **by comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of said conserved region**" (emphasis added). Appellant's undersigned representative has not been able to locate any portion of the cited references which teach these features.

The Office asserts that:

> Hentze et al. compares the human sequence to orthologous sequences from other species in figure 2 and the discussion on page 1572 and concludes that the sequence is highly conserved during evolution.

(See, page 6 of the Final Rejection). The Hentze reference, however, does not teach or suggest identifying *in silico* at least one molecular interaction site less than 30 nucleotides in length on said human target RNA **by comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of said conserved region**" (emphasis added). Rather, the Hentze reference identified the IRE by constructing a series of deletion mutants and examining for the presence of iron responsiveness. The IRE was, in fact, identified by adding back a fragment to an iron-nonresponsive construct and looking for the rescue of iron responsiveness (see, entire Hentze reference). The portion of the Hentze reference relied upon in the Final Rejection does not support the assertion that the molecular interaction site was **identified** by "comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of said conserved region." Rather, the portion of the Hentze reference actually reports:

> Comparison of the core region of the human ferritin H-chain cDNA leader sequence (which contains the IRE) with the leader sequences of the human ferritin L-chain (15) and the cDNA sequences of ferritins from other species (16, 17), reveals that the core region of the predicted stem-loop structure has been highly conserved during evolution. This sequence predates the evolutionary segregation between amphibians, birds, and man which occurred more than 300 millions years ago (17).

(See, page 1572, middle column of the Hentze reference). This portion of the Hentze reference certainly does not support the allegation that the molecular interaction site was identified by "comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of said conserved region." Rather, after the IRE sequence was identified by construction of deletion mutants and examining for iron responsiveness, it was further characterized by the described evolutionary analysis. Thus, even if the cited references are combined in the manner suggested by the Office, the invention recited in claim 26, as well as claims dependent thereon (i.e., claims 30, 40, and 41), is not produced.

The Office also fails to make out a *prima facie* case of obviousness in regard to the remaining independent claims. When making a *prima facie* case of obviousness, it remains necessary to identify some reason that would have led a person skilled in the art to modify the teachings of a reference in a particular manner. *Takeda Chemical Industries, Ltd. v Alphapharm Pty. Ltd.*, 492 F.3d 1350, 83 USPQ.2d 1169 (Fed. Cir. 2007). No such reasoning has been provided. The Office asserts that "[I]t would have been further obvious to use mass spectroscopy to analyze binding strength because Sezerman shows that peptides may be analyzed in silico for binding, and Greig et al. shows that mass spectroscopy may be used to determine the binding affinity of a complex of a peptide and an oligonucleotide…" (see, Final Rejection at pages 6-7).

The Sezerman reference reports computational determination of peptide-receptor structure using a docking computer program whereby conformationally flexible ligands are docked to a receptor. Interaction energy was calculated using CHARMm, which is a computer program. Thus, the Sezerman reference uses an entirely *in silico* method to dock ligands to a receptor and calculate the interaction energy of such docking. The Sezerman reference does not teach or even suggest replacing the CHARMm interaction energy calculating program with any

other method of analyzing binding affinity, let alone an actual bench method, let alone mass spectrometry. Indeed, a goal of the Sezerman reference is to perform computational determination of peptide-receptor structure. Replacement of the CHARMm method of determining interaction energy between a peptide and a receptor with a mass spectrometric method of determining binding strength between an oligonucleotide and a serum albumin (as reported in the Greig reference) is nonsensical and defeats a goal of the Sezerman reference, i.e., a computational method of peptide-receptor structure. It is only upon examination of Appellant's specification that such claimed methods can be rendered obvious. Appellant respectfully points out that "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ.2d 1780, 1784 (Fed. Cir. 1992).

In addition, if a proposal for modifying the prior art in an effort to attain the claimed invention causes the art to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. *See In re Fritch*, 972 F.2d at 1265 n.12 ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose."); *In re Ratti*, 270 F.2d 810, 813 (CCPA 1959) (holding the suggested combination of references improper under §103 because it "would require a substantial reconstruction and redesign of the elements shown in [a prior art reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate"). In this regard, the Murray reference reports an *in silico* method of identifying virtual compounds that can bind to a particular site within a molecule. The Murray reference reports identification of thrombin inhibitors by a completely *in silico* method, in contrast to actually carrying out physical binding assays. Thus, a major goal of the Murray reference is to provide an *in silico* method, rather than actual physical methods, of predicting binding of a potential therapeutic compound to a particular receptor. Any modification of the Murray reference that would add another layer of a completely different, let alone physical, technology such as mass spectrometry, would be counter to the *in silico* methodology of the Murray reference. Therefore, the requisite motivation to further modify the methodology of the Murray reference does not exist. In this regard, each of claims 19 (and dependent claims 20, 37, and 38), 32 (and dependent claims 33, 43, and 44), and 34 (and dependent claims 35, 46,

and 47) recite "testing said highly ranked members to determine their ability to interact with said molecular interaction site by: contacting the human target RNA with at least one of said highly ranked members to provide a complex between the human target RNA and the member or members; ionizing said complex; fragmenting the ionized complex; and determining whether highly ranked members bind to the molecular interaction site of said human target RNA" or similar variation thereof, and therefore are not obvious over the combination of cited references.

The Office responds by asserting that "the in silico and experimental approaches of these two references [the Murray and Greig references] are not in conflict, the two references show complementary methods of studying formation of binding complexes, each with advantages such as speed and ability to assay a large range of potential compounds for the in silico method, and accuracy and experimental confirmation of predicted complex formation for the mass spectrometry method" (see, Final Rejection at page 7). These observations by the Office, however, do not address the issue raised by Appellant. Indeed, the Office's proposal to modify the methodology of the Murray reference in an effort to attain the claimed invention destroys one intended function and requires a substantial reconstruction and redesign of the elements shown in the Murray reference as well as a change in the basic principles under which construction was designed to operate, i.e., in an *in silico* environment.

In view of the foregoing, Appelllant's claimed invention is not obvious in view of the picking and choosing and subsequent recombination of portions of five references. Accordingly, Appellant respectfully requests that the rejection under 35 U.S.C. §103(a) be reversed.

VIII. Claims Appendix

The following claims are on appeal:

19. A method of identifying a compound that binds to a human target RNA comprising:

generating *in silico* a virtual library of compounds and an *in silico* three dimensional representation of a molecular interaction site within said human target RNA, wherein the molecular interaction site is less than 30 nucleotides;

comparing *in silico* said three dimensional representations of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site;

synthesizing the highly ranked members of said hierarchy of compounds; and

testing said highly ranked members to determine their ability to interact with said molecular interaction site by:

contacting the human target RNA with at least one of said highly ranked members to provide a complex between the human target RNA and the member or members;

ionizing said complex;

fragmenting the ionized complex; and

determining whether highly ranked members bind to the molecular interaction site of said human target RNA; and

thereby identifying said compound that binds to a human RNA target.

20. The method of claim 19 further comprising determining the strength of binding of a highly ranked member in comparison to the binding strength of other highly ranked members.

26. A method of identifying a compound that binds to a human target RNA comprising:

identifying *in silico* at least one molecular interaction site less than 30 nucleotides in length on said human target RNA by comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species;

identifying at least one conserved region, and determining the secondary structure of said conserved region;

generating *in silico* a virtual library of compounds predicted or calculated to interact with said molecular interaction site;

comparing *in silico* three dimensional representation of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site;

synthesizing the highly ranked members of said hierarchy of compounds;

testing said highly ranked members to determine their ability to interact with said molecular interaction site;

contacting said human target RNA with at least one of said highly ranked members to provide a complex between said human target RNA and the member or members;

ionizing said complex;

fragmenting the ionized complex; and

determining whether highly ranked members binds to the molecular interaction site of said human target RNA; and

thereby identifying; said compound that binds to a human RNA target.

30. The method of claim 26 further comprising determining the strength of binding of a highly ranked member in comparison to the binding strength of other highly ranked members.

32. A method of identifying a compound that binds to a human target RNA comprising:

identifying at least one molecular interaction site on said human target RNA, wherein the molecular interaction site is less than 30 nucleotides;

generating *in silico* a virtual library of compounds predicted or calculated to interact with said molecular interaction site;

comparing *in silico* three dimensional representations of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds

ranked in accordance with their respective ability to form physical interactions with said molecular interaction site;

synthesizing said highly ranked members of said hierarchy of compounds;

contacting said human target RNA with at least one of said highly ranked members to provide a complex between said human target RNA and said member or members;

ionizing said complex;

fragmenting said ionized complex; and

determining whether highly ranked member or members bind to said molecular interaction site of said human target RNA;

thereby identifying said compound that binds to a human RNA target.

33. The method of claim 32 further comprising determining the strength of binding of at least one highly ranked member in comparison to the binding strength of other highly ranked members.

34. A method of identifying a compound that binds to a human target RNA comprising:

identifying at least one molecular interaction site of less than 30 nucleotides on said human target RNA, wherein said human target RNA comprises single-stranded RNA and is mRNA, premRNA, tRNA, rRNA, or snRNA;

generating *in silico* a virtual library of compounds predicted or calculated to interact with said molecular interaction site;

comparing *in silico* three dimensional representation of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site;

synthesizing the highly ranked members of said hierarchy of compounds;

contacting said human target RNA with at least one of said highly ranked members to provide a complex between said human target RNA and the member or members;

ionizing said complex;

fragmenting said ionized complex; and

determining whether highly ranked member or members binds to said molecular interaction site of said human target RNA;

thereby identifying said compound that binds to a human RNA target.

35. The method of claim 34 further comprising determining the strength of binding of at least one highly ranked member in comparison to the binding strength of other highly ranked members.

37. The method of claim 19, wherein said molecular interaction site comprises a secondary structure selected from a bulge, a loop, a stem, a hairpin, or a mismatch basepair.

38. The method of claim 37, wherein said secondary structure is located within an untranslated region of said human target RNA.

40. The method of claim 26, wherein said molecular interaction site comprises a secondary structure selected from a bulge, a loop, a stem, a hairpin, or a mismatch basepair.

41. The method of claim 40, wherein said secondary structure is located in an untranslated region of said human target RNA.

43. The method of claim 32, wherein said molecular interaction site comprises a secondary structure selected from a bulge, a loop, a stem, a hairpin, or a mismatch basepair.

44. The method of claim 43, wherein said secondary structure is located in an untranslated region of said human target RNA.

46. The method of claim 34, wherein said molecular interaction site comprises a secondary structure selected from a bulge, a loop, a stem, a hairpin, or a mismatch basepair.

47. The method of claim 46, wherein said secondary structure is located in an untranslated region of said human target RNA.

IX. Evidence Appendix

None.

X. Related Proceedings Appendix

None.

Conclusion

All rejections of the pending claims are improper and should be reversed. For the reasons given above, appealed claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 are patentable.

Respectfully submitted,

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